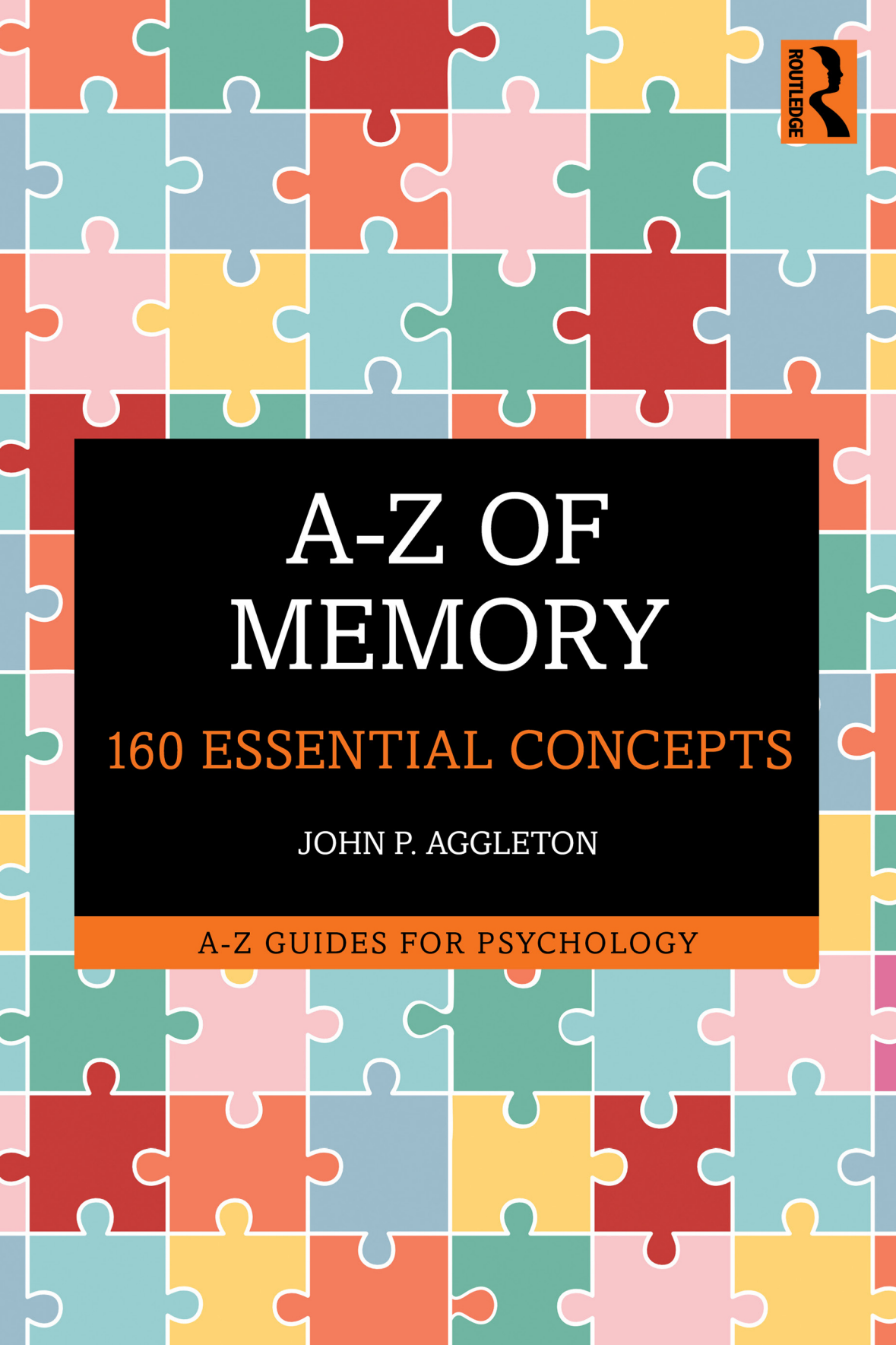
ROUTLEDGE
A-Z OF MEMORY
160 ESSENTIAL CONCEPTS
JOHN P. AGGLETON
A-Z GUIDES FOR PSYCHOLOGY

A–Z of Memory

This book compiles and explains the key terms and core concepts related to memory in an easy-to-navigate A–Z format.

The quest to understand how memory works and how it fails remains a cornerstone of both Psychology and Neuroscience. That quest begins with an appreciation of the many faces of memory. For some, memory is largely seen as a means to preserve information while others emphasize the significance of remembering. In this innovative book, John Aggleton delves into the many properties of memory and guides the reader through over 160 entries ranging from Aging to Repression; Dementia to Working Memory. Each entry explores the various psychological and biological elements of memory and includes recommended further reading and cross-referencing.

This guide will serve as an overview and introductory resource for students and scholars involved in memory studies and memory research, as well as practitioners working with sufferers of memory disorders. It will also be of great interest to anyone interested in the utterly remarkable memory skills we all possess.

John Aggleton is a world-wide recognized researcher and author. He has published over 300 papers, principally on brain systems devoted to different forms of memory. His contribution to the field was recognized by the Royal Society in 2012 when he was elected as a Fellow. He has also served as President of the British Neuroscience Association and of the European Brain and Behaviour Society. He is currently Emeritus Professor of Cognitive Neuroscience at Cardiff University.

A–Z Guides for Psychology

The series *A–Z Guides for Psychology* provides accessible, easy-to-navigate overviews of a range of different topics related to all aspects of psychological research. Following an A–Z format, each book contains entries that map out an important concept or term and illustrate how it connects more broadly to other ideas and disciplines.

The series *A–Z Guides for Psychology* will be of great interest to students, scholars and practitioners learning, teaching and researching in this field.

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A–Z of Memory

160 Essential Concepts

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Introduction

This book is unique among texts on memory. With over 160 alphabetical entries, a host of separate topics are placed at your fingertips. Each entry explains a different aspect of memory – some you may anticipate, others may come as a complete surprise. Memory is explored from the level of the single neuron to the whole organism. Concepts from both cognitive psychology and neuropsychology are described, as well as those from comparative psychology.

Should you be in any doubt about reading this book, remember just how much memory matters. We are each the sum of our unique memories. But our memories do not just represent the past; they also guide us through the present and into the future. Surely it is worth finding out as much as possible about the many different facets of memory.

This book examines those memories possessed by biological organisms, with human memory at the forefront. While we may readily use terms such as 'computer memory' and 'memory stick', not to mention 'memory foam' or even 'memory metal' (which will spontaneously return to its original, complex shape after being bent), these borrowed usages are not included.

Even with these exclusions, the term 'memory' remains imprecise and can be interpreted in different ways. To anticipate this problem, it is presumed here that 'memories' are: 1) confined to animals that have neurons, 2) involve the formation of an internal representation, 3) require that this representation can outlast the initial sensory or cognitive experience, and 4) that there is the potential for that representation to effect change.

There is, however, one entry that provides an exception to these memory criteria. That entry discusses the possibility of plant memory as well as claims of memory in some unicellular organisms, even though they lack neurons. (The truly remarkable abilities of some slime moulds, which may come as a complete surprise, fully deserve their inclusion in this book.)

First and foremost, the book is a comprehensive source to reach for when needed or when curious. Each entry starts with a brief definition followed by a self-contained description that considers the topic in depth. Related topics that are detailed elsewhere in the book are *flagged in italics*, giving the reader a broader

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understanding while also limiting any duplication. References at the end of each entry back up the content and provide scope for further reading. For those topics with more than one potential title, alternative titles are listed alphabetically in the Table of Contents and the reader directed to the principal entry. (Lastly, should you wonder, none of the content was generated by AI.)

A

ABSENT-MINDED – *being forgetful, often from a failure to pay attention to one's actions*

Absent-mindedness is a major cause of forgetting (Schacter, 2022). Causes of absent-mindedness include being distracted or preoccupied, leading to mind wandering. A lapse of attention, even one that is very brief, is often more than enough to cause an everyday memory failure. Furthermore, a little lapse in attention may lead to bigger lapses that, in turn, may encourage daydreaming or feelings of boredom (Cheyne et al., 2006). A consequence is that information is poorly processed and vulnerable to forgetting. Distracted thinking can have the same result.

A frequent example is being unsure on whether you just locked the car (or the house). The action of locking is largely automatic and typically involves little attention. At the same time, we are often preoccupied with thoughts about what we should be doing next. A further complication is the need to separate today's actions from very similar actions on previous occasions (*Interference*). The ability to remember to execute a planned future action (see *Prospective Memory*) is also highly prone to absent-mindedness, especially when there are no external cues to prompt that action, be it posting a letter, taking a pill, or having the car serviced.

There is a strong link between absent-mindedness, attention, and shallow processing (see *Elaborative rehearsal*). The ways in which we engage with information make an enormous difference to its memorability. There are many factors that affect memorability, but a principal one is the ability to comprehend information and appreciate its implications, sometimes called deep or elaborative rehearsal. In contrast, absent-mindedness is often accompanied by superficial processing. Exacerbating factors include mind-wandering, a lack of sleep, being distracted, or the fact that the information to be remembered is part of a well-rehearsed routine.

Multi-tasking can often lead to absent-mindedness. Famously, the Greek philosopher Thales is supposed to have fallen down a well when walking and, at the same time, admiring the night sky. There is a tendency in literature to think of absent-mindedness as an endearing characteristic. Examples include preoccupied professors such as Albus Dumbledore from the Harry Potter books and 'Doc' Emmett Brown from the 'Back to the Future' films. Alas, absent-mindedness has its dark side. It is one of the principal reasons given when people feel wrongly accused

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of shop-lifting (Reason & Lucas, 1984). Very sadly, drivers have been known to forget that they have a baby or a pet in the back seat, only to leave them in the car with closed windows on a hot day.

For actions that are regularly associated with memory failure, such as locking the house, there are solutions. One approach is to have a concrete image tied to the action of locking the door, and then later recalling that thought or image to confirm your action. (But not the same image every time.) Technology, such as smart phones, can cause distractions that increase absent-mindedness, but can also create the opportunity to post reminders or cues that help to combat forgetfulness.

Cheyne, J. A., Carriere, J. S., & Smilek, D. (2006). Absent-mindedness: lapses of conscious awareness and everyday cognitive failures. *Consciousness and Cognition*, *15*(3), 578–592.

Reason, J., & Lucas, D. (1984). Absent-mindedness in shops: its incidence, correlates and consequences. *British Journal of Clinical Psychology*, *23*(2), 121–131.

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ADAPTIVE MEMORY – *that our learning and memory skills are tuned to solving fitness-based problems, reflecting how our memory evolved*

The evolutionary-based concept of 'adaptive memory' has its origins in earlier attempts to explain why some associations seem disproportionately easier than others. One such attempt invoked the idea of cognitive 'preparedness'. That term was used to explain why certain species seem especially prepared to learn specific associations. For instance, if the consumption of a food or drink is followed by nausea, the unfortunate sufferer may acquire a persistent *Conditioned taste aversion*. This learning exemplifies 'preparedness' as the resulting taste avoidance is unusually persistent and is typically far greater to the taste rather than the visual appearance of the offending food or drink. Likewise, phobias overwhelmingly apply to just a small, select list of stimuli (such as snakes, spiders, and enclosed spaces) even though our present environment contains many far more dangerous things that need to be avoided (Öhman & Mineka, 2001).

Like 'preparedness', the concept of 'adaptive memory' starts with the premise that memory processes have been subject to natural selection. This evolutionary perspective leads to the not unreasonable conclusion that our current memory characteristics retain elements that reflect ancestral selection pressures. Consequently, organisms have evolved individual memory systems that are geared to keep species-appropriate survival and fitness-related information which, thereby, enhances their reproductive fitness (Nairne, 2010). One potential side effect is that while our adaptive memories may increase the remembrance of true survival-related items, they can also increase the false recall of such items.

When we consider *Homo sapiens*, the focus is on the evolutionary changes that took place long ago in an African environment, a location that is now very distant for a great many people. The prediction is that we should retain

an enhanced sensitivity to certain types of historic information that is domain-specific, even though evolutionary pressures have since shifted. Those domains of adaptive memory should relate to topics such as survival (e.g., food sources, predators, medicines, weather patterns, and shelter), navigation, reproduction, social exchange, and kinship, all topics of considerable relevance for biological fitness.

One of the initial studies promoting the concept of adaptive memory used a variety of *Incidental learning* tasks in which people rated common nouns for their relevance to personal survival, such as gathering food or finding shelter (Nairne et al., 2007). In the control conditions the same words were rated for their pleasantness, their relevance to moving between countries, or their personal significance. In a surprise memory test for those same nouns, participants showed a 'survival advantage'. Those who performed best (recall and recognition) had rated the words for their survival relevance. The adaptive memory explanation is that those words were the most likely to be retained given our ancestral environment and its challenges, such as living on the savannah and avoiding predators. Their remembrance would have benefitted from the presence of memory modules that are tuned for processing and remembering information that historically aided survival.

Other potential examples of adaptive memory include our superior memory for animate over inanimate stimuli. At the same time, comparative research has highlighted neuroanatomical specializations in those animal species that face very specific memory demands, such as those found in bird species that cache large quantities of food. Further examples include '*Imprinting*', in which a newly born animal, such as a duck or goose, displays a sensitive period during which they become strongly attached to what should be their parent.

Adaptive memory has gained considerable interest in recent years with speculations on how past evolutionary pressures have left a mark on almost all aspects of our current memory capabilities (Murray et al., 2020). While there can be no doubt that evolution has altered our brains as well as our bodies, the adaptive memory hypotheses highlights elements we have retained even though those past evolutionary pressures are now relaxed. Meanwhile, neuroscientific investigations suggest that dopamine interactions within the hippocampus support functions consistent with adaptive memory. In particular, that dopamine biases our memory towards events that have motivational significance (Shohamy & Adcock, 2010).

Murray, E. A., Wise S. P., & Baldwin, M. K. L. (2020). *The Evolutionary Road to Human Memory*. Oxford University Press.

Nairne, J. S. (2010). Adaptive memory: evolutionary constraints on remembering. In *Psychology of Learning and Motivation* (vol. 53, pp. 1–32). Academic Press.

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AGING – *the impact of time on an organism once maturity is reached*

Depending on your definition, aging may start from birth, or even from conception, but here the focus is on what happens once maturity is reached. Thereafter, aging is often seen as a loss of function over time alongside the gradual accumulation of damaging changes. Studies that track changes in memory performance across one's lifetime confirm that healthy aging is typically associated with a decline in various forms of memory. Aging is also the biggest risk factor for many neurological disorders, including those *Dementias* that impact on memory.

All forms of memory are susceptible to aging, but at different rates. Data from *Longitudinal studies* show that *Semantic memory* (our memory for factual information that is often shared with others) is one of the most resilient types of memory. On average, performance on semantic memory tasks continues to improve across mid-life and does not peak until we are in our 60s but may then deteriorate for those in their 70s and above (Nyberg et al., 2012). In contrast, *Episodic memory* (our memory for individual day-to-day events) often begins to decline when we are in our 60s (Nyberg & Pudas, 2019). *Autobiographical memory*, which concerns our personal histories and involves both episodic and semantic memory, also declines with aging. As it does, there is a shift from episodic to more fact or gist-like recollections, a process called 'semantization' (Frankenberg et al., 2022).

Meanwhile *Working memory* can decline from our mid-50s (working memory refers to our on-line thoughts and their cognitive control), a decline that can be associated with age-related brain changes (Chai et al., 2018). Age-related difficulties with working memory are often more pronounced for tasks that require updating and switching, as well as inhibiting attention. A contributing factor is that the elderly can find it more difficult to supress irrelevant items (Rowe et al., 2008). Some forms of *Implicit memory*, such as *Priming*, can appear to be unusually resilient to aging, although the degree of preservation differs for the various forms of priming and some impairments may, in part, reflect encoding difficulties (Ward, 2024). Other types of implicit memory, such as eye-blink *Classical conditioning*, may start to decline after we reach our 60s. The vulnerability of classical conditioning may well relate to the loss of integrity in brain structures that include the cerebellum and the hippocampal formation (Woodruff-Pak, 2001).

There is considerable individual variation in memory performance as we age, and the extent of this individual variation increases across the advancing decades. Those who seem least affected by aging have been described as 'super-agers'. This term is usually reserved for those who show a relative preservation of episodic memory. Meanwhile, those showing signs of more obvious, premature memory decline will include people with *Mild Cognitive Impairment*, along with those in the initial stages of dementing disorders, including *Alzheimer's disease*.

The proportion of super-agers in the population depends on the criteria used (Nyberg & Pudas, 2019). One definition is that the term applies to older adults who both perform at or above the mean level for younger adults and maintain that level over time. For example, a population study from Sweden initially identified about 8.0% of those over 70 years old as performing at or above the level for much

younger adults. However, only a third of these same individuals maintained this level five years later (now aged 75–90). By these strict criteria, true super-agers may comprise less than 3% of the population (Habib et al., 2007).

Super-aging is associated with higher I.Q. and more years of education. These associations are thought to reflect the possession of greater 'cognitive reserve'. The term 'cognitive reserve' refers to the ability to employ efficient cognitive and neural strategies to counter the effects of aging. Evidence for cognitive reserve comes from comparisons of individuals with seemingly comparable brain health yet different rates of cognitive decline with age.

The other contributing element to super-aging is 'brain reserve'. This term relates to the physical status of the brain, and how it differs from person to person. With respect to memory, two parallel sets of processes are presumed to determine levels of brain reserve (Nyberg et al., 2012). The first process concerns the widespread depreciation of both grey and white matter that can occur across the brain with increased aging. It is known that both brain volume and cognitive ability diminish during normal aging. One estimate is that for those over 50 years-old, cortical volumes decrease by about 5% every decade. Meanwhile, estimates of the total length of the nerve axons in our brains point to a more rapid decrease of about 10% every decade from adulthood (see *White matter plasticity*).

The second aspect of brain reserve concerns the vulnerability of those structures that are especially critical for normal memory. For instance, hippocampal atrophy is a frequent feature of aging, with its different subfields showing varying rates of cell loss. This atrophy is associated with a decline in episodic memory (Nyberg, 2017). Another brain region that often shows a disproportionate degree of shrinkage with aging is the prefrontal cortex, which has important *Executive functions* that influence memory, including the recall of episodic memory. The fornix, a fibre tract that links the hippocampus with many sites, including the prefrontal cortex, also displays age-related changes that correlate with episodic memory (Metzler-Baddeley et al., 2011). These various changes help to explain why episodic memory can be so vulnerable to aging as it involves multiple processes that depend on a range of structures that are themselves vulnerable to the effects of aging (Nyberg, 2017).

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ALCOHOL – *a chemical (ethanol) with psychoactive effects that is globally used as a recreational drug*

Almost every civilization across the world seems to have discovered alcohol. It is thought that forms of wine or beer were created as long as eight thousand years ago. Currently, around 70% of all adults in Europe and North America have consumed alcohol at least once in the preceding year. In contrast, levels of alcohol intake in the Middle East and North Africa are far lower, at around 5%.

Alcohol (ethanol) at moderate levels disrupts most brain functions, including memory. Its wide array of acute actions include changes to glutamate receptors (most notably NMDA receptors) as well as to GABA and cholinergic interneurons. Alcohol also affects dopamine and various ion-channels. These primary actions then have a cascade of secondary effects on neural activity. Exposure to alcohol also alters the function of proteins involved in synaptic transmission. While alcohol is chiefly seen as a neural depressant as acute alcohol reduces overall brain metabolic levels, this is not true for all areas. For example, functional imaging reveals that while certain structures, such as the cerebellum, decrease their activity, the ventral striatum can show increased activity associated with greater dopamine availability. This latter response is related to the hedonic and addictive aspects of alcohol (Engel & Jerlhag, 2014).

Acute alcohol affects multiple psychological functions. Of these, attention, visuo-motor control, and aspects of emotion are especially sensitive. Alcohol's direct and indirect effects on memory result in impaired encoding, consolidation, and retrieval. The breadth of its actions means that acute alcohol can disrupt working memory, episodic memory, and semantic knowledge, i.e., all elements of explicit memory (Mintzer, 2007). As alcohol levels rise, plasticity within key brain areas such as the hippocampus becomes increasingly vulnerable. One consequence is the failure to link and store ongoing events with their appropriate contextual signals. To compound matters, alcohol disrupts sleep, which may further impair memory consolidation.

In addition, changes in one's internal state caused by alcohol can lead to *Context-dependent memory* problems. As a result, it becomes more difficult, when under the influence of alcohol to recall events that occurred when sober (and *vice versa*). The same effect helps to explain one of the more surprising findings concerning alcohol – a specific scenario in which alcohol can sometimes improve memory. When the learning of information is followed by a modest dose of alcohol, the delayed recall

of that initial information can sometimes be enhanced ('retrograde facilitation'). One explanation is that the alcohol reduces the impact of memory interference during the retention period, thereby protecting the learning. This reduced interference stems from the change in state induced by the alcohol (Quevedo Pütter & Erdfelder, 2022). Meanwhile, other explanations for retrograde facilitation focus on memory consolidation.

In contrast to its overwhelmingly disruptive effects on explicit memory, acute alcohol appears less disruptive to some aspects of *Implicit memory* such as *Priming* (Mintzer, 2007). This difference is highlighted by studies showing that acute doses of alcohol can impair recollective-based recognition but spare repetition priming for the same information. Nevertheless, animal studies show that acute alcohol can disrupt various classical conditioning tasks as well as different forms of habituation, both forms of implicit memory.

A disturbing consequence of consuming high levels of ethanol is the alcoholic blackout. This alarming event can happen if a large amount of alcohol is drunk over a short time period. It is thought that of those college students who consume alcohol, between a third and a half will, at some point, experience an alcoholic blackout. Importantly, a blackout is not the same as passing out. A blackout occurs when you have no explicit memory for a past intoxicated period, despite remaining conscious throughout. Consequently, the episodic memories for that period are lost.

During an alcoholic blackout, access to semantic information is reduced. Nevertheless, people remain able to interact and will carry on conversations, even though those same experiences will later be lost from memory. The resulting blackout can be complete for a specific period ('en bloc') or it may be partial ('fragmentary'). En block memory loss is usually permanent, so that trying to jog your memory with cues does not help.

Blackouts do not happen every time someone is drunk. They are closely associated with a rapid rise of blood alcohol. Consequently, speedy drinking on an empty stomach, especially when consuming spirits, is most commonly associated with a blackout. Related risk factors include a history of binge drinking, previous blackouts, and prior head injuries. There may also be a genetic predisposition to suffering blackouts. Overall, women are more susceptible to alcoholic blackouts and show a slower recovery from the impact of alcohol on cognition. This greater sensitivity may reflect sex differences in the transfer and clearance of alcohol.

The chronic consumption of excessive alcohol is highly detrimental. Alcohol addiction is often seen as a switch in the brain's mechanisms that are related to learning and hedonics. In particular, there is thought to be a shift from goal-directed behaviours that encourage controlled drinking to habit learning, which encourages dysregulated, uncontrolled drinking. The neural basis of this shift is thought to be located within striatal brain systems (Van Skike et al., 2019).

The neural damage caused by alcohol stems from a combination of factors, including increased neuroinflammation and blood vessel damage. Furthermore, the chief metabolite of alcohol (acetaldehyde) is neurotoxic. These damaging effects are hastened by how alcohol increases the permeability of the blood brain barrier (which protects the brain's milieu). Chronic alcoholics may suffer vitamin B1

deficiency (thiamine), which results in brain pathology (see *Korsakoff's disease*). These damaging effects may be further exacerbated by head injury, a common risk associated with excessive drinking.

Alcohol-related neurological disorders include alcoholic dementia, Wernicke's disease, and the amnesic Korsakoff's disease. People suffering from alcoholic dementia have memory difficulties alongside problems in negotiating complex tasks that require planning and forethought. The severity of these difficulties can vary from mild to severe, i.e., it is not an all-or-none disorder.

Wernicke's disease (encephalopathy) and Korsakoff's disease can occur separately or in combination. Wernicke's encephalopathy often has a sudden onset and is characterized by movement and balance problems, a loss of coordination and gait, confusion, disorientation and abnormal eye movements. The onset of Korsakoff's disease is usually more gradual, the sufferer displaying poor attention and concentration. The most striking symptom, however, is the loss of autobiographical memory, creating extensive memory blanks that are sometimes filled in inaccurately (see *Confabulation*). This loss of past information can extend back decades. At the same time, the learning of new information that would normally enter long-term memory is severely compromised. The condition is often permanent.

Finally, alcohol is also a risk factor for *Alzheimer's disease*. Previous claims that low levels of red wine might be protective have largely been disproved. The reality is that no level of alcohol is beneficial for brain health (Nutt et al., 2021). Both heavy and moderate alcohol intake is associated with decreases in global brain volume and regional grey matter volumes, as well as changes to white matter microstructure. These negative associations are already present in those consuming an average of only one to two alcohol units daily, becoming stronger as regular alcohol intake increases.

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ALZHEIMER'S DISEASE – *the commonest form of dementia characterized by the presence of brain atrophy, amyloid plaques, and neurofibrillary tangles, along with pronounced cognitive decline*

Alzheimer's disease, the most frequent form of dementia, presents a global challenge of catastrophic proportions. Given an increasingly aging population worldwide, it has been estimated that by 2050, the prevalence of *Dementia* will double

in Europe and triple worldwide, resulting in around 150 million cases (Scheltens et al., 2021). Of these cases, 60–70% will suffer from Alzheimer's disease.

Early symptoms of Alzheimer's disease include a loss of episodic memory (a failure to remember recent past events) and difficulties with prospective memory (a failure to remember future tasks). Another aspect is the early impact on verbal fluency and naming, which can be the first indications that semantic memory is starting to deteriorate (Verma & Howard, 2012). These language difficulties may be present long before formal diagnosis. Working memory is also disrupted. As the disease progresses, the loss of semantic memory becomes more pervasive while aspects of implicit memory also become affected. The illness affects both the retrieval of past autobiographical memories, as well as the formation of new memories. However, the impact of the disease is not confined to memory, and so its diagnosis includes the chronic disruption of other cognitive skills. This broader picture includes disorders of attention, which contribute to difficulties with working memory and episodic memory (Malhotra, 2019).

The disease was first formally described by Alois Alzheimer in 1906. He observed the brain's accumulation of protein plaques and neurofibrillary tangles that are characteristic of this type of dementia. However, it was not until the 1960s that the true frequency of Alzheimer's disease began to be appreciated. It is now known that about one person in 14 over the age of 65 has a form of dementia, with the proportion rapidly rising with advancing age. Of these, about two-thirds will have Alzheimer's disease. The disease is often subdivided between those with 'early-onset' (before 65 years of age) and late-onset Alzheimer's disease (LOAD). The early-onset variant typically has a stronger genetic basis.

Diagnosis initially relies on cognitive testing. Favoured cognitive tests are the Mini-Mental State Examination (MMSE) and the MoCA (Montreal Cognitive Assessment). A score of 23 or less on the MMSE is usually seen as an indicator of dementia, although upward adjustments should be made for those with high levels of education/high I.Q. Of the various MMSE subtests, it is thought that temporal orientation, delayed recall, attention/concentration, and copying geometric drawings may be the most sensitive. Other sensitive tests tax spatial learning and memory.

In reality, a large number of other dementias affect cognition, and so a variety of biomarkers are needed to confirm the diagnosis of Alzheimer's disease. Structural MRIs reveal both cortical and subcortical atrophy, which is often especially pronounced in the medial temporal lobe. At the same time, there is ventricular enlargement (Figure A.1). Other biomarkers include raised levels of the protein beta amyloid (β amyloid or Aβ) and increased levels of the protein Tau. Beta amyloid is a major component of plaques, while Tau proteins form the characteristic neurofibrillary tangles that develop inside neurons.

It is now known that Alzheimer's disease has a long 'prodromal' (hidden) phase when few, if any, cognitive symptoms are apparent. The disease may well begin 25–30 years before any final diagnosis, meaning that its true beginnings are when people are in their forties and early fifties. At this preclinical 'at-risk' stage there is an increased accumulation of β amyloid and Tau protein, but no cognitive

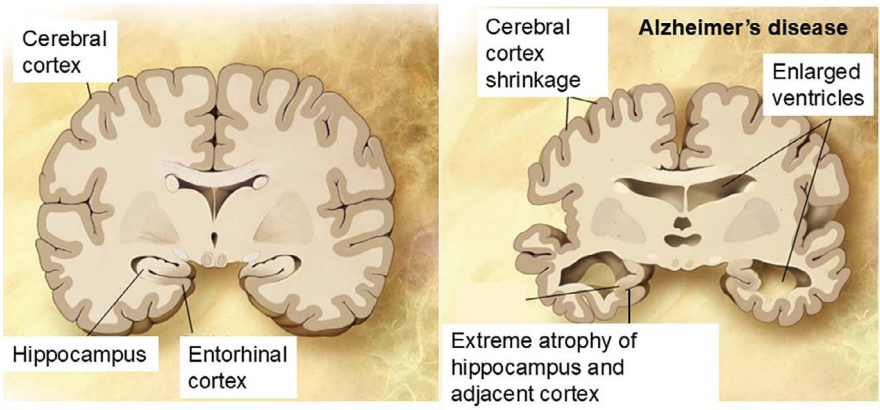

Figure A.1 Alzheimer's disease. Comparison of normal brain (left) and atrophied brain associated with Alzheimer's disease (right), displaying cortical and subcortical shrinkage alongside ventricular enlargement.

symptoms. Clearly, there is a need for accurate early diagnosis so that mitigating treatments can begin as early as possible (Porsteinsson et al., 2021).

Detecting the biomarkers for Alzheimer's disease is both time-consuming and costly, leaving the process available to only a minority of sufferers. At the same time, Alzheimer's disease is a global-wide disorder with a terrible human cost. Consequently, practical, affordable methods of diagnosis are a high priority. Increasingly effective blood tests have recently been developed to diagnose this disease. These tests often look at the ratio of two types of amyloid beta, along with the proportion of Tau that is phosphorylated (e.g., p-Tau217). (The term 'phosphorylated' indicates the addition of a phosphorous group, which alters the conformation of Tau and, hence, its properties.) The rationale for the Tau marker stems from the realization that Tau hyperphosphorylation is a key pathological feature.

Alzheimer's disease is a progressive disorder that advances at differing speeds across individuals and disproportionately affects certain brain sites. One of the earliest regions to be affected is the medial temporal lobe, including the parahippocampal cortex, along with the hippocampus and amygdala. It is, therefore, no surprise that episodic memory, which relies on hippocampal integrity, is often an early victim of Alzheimer's disease. Other early vulnerable sites include the retrosplenial cortex and anterior thalamus, both part of a network of brain structures that, along with the hippocampus, are crucial for spatial processing as well as episodic memory. Consequently, people in the early stages of Alzheimer's disease are at greater risk of becoming disorientated and finding themselves lost. Indeed, tests of spatial navigation may offer a route to identify preclinical and prodromal disease states (Coughlan et al., 2018).

Initially, a person with Alzheimer's disease will show modest cognitive deficits. At this stage, the sufferer is likely to be diagnosed as having *Mild Cognitive Impairment* (MCI). Mild Cognitive Impairment is found in 10–20% of those aged

over 65, of which around one half will develop Alzheimer's disease over the following 5–10 years. As you might expect, some of the most typical symptoms of MCI are a loss of episodic memory, problems with getting lost, and failures of prospective memory. Working memory also starts to fail. This decline is most obvious for dual tasks that make simultaneous demands on different cognitive processes.

The extent of cortical and subcortical pathology continues remorselessly in Alzheimer's disease. Not only do existing memory problems become worse, but there are more and more failures of semantic memory, affecting knowledge and language. There is a common belief that memories from childhood and one's youth are better protected from the disease. Formal tests sometimes show a relative sparing of early episodic and factual autobiographic information, but this is not a reliable pattern (Meeter et al., 2006). The extent of any saving does appear to partly depend on the type of memory test used to assess old autobiographical memories.

Despite decades of intensive research, there is currently no cure for Alzheimer's disease. The recent development of immunotherapies that target amyloid protein may help to slow down disease progression by about 25% for those in the early stages of the disease. Clearly there is still a long way to go, with future therapeutic interventions turning to Tau protein, in combination with β amyloid clearance, while also needing to address the contributions from neuroinflammation (Heneka et al., 2024).

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AMNESIA – *the loss of memory despite the sparing of other cognitive abilities*

It is believed that amnesia was first designated as a specific medical disorder in 1763 by François Boissier de Sauvages (Langer, 2021). It is not a unitary condition as there are many different forms of amnesia (Markowitsch & Staniloiu, 2012).

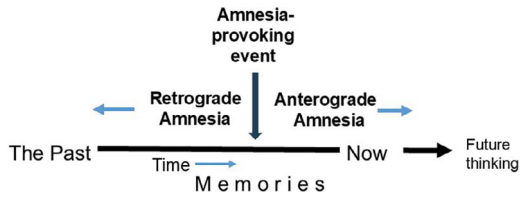

Figure A.2 Amnesias can be anterograde (new memories lost), retrograde (old memories are lost), or both. The ability to envisage future memories is also often affected in anterograde amnesia.

One major cause is traumatic or neuropathological damage to the brain ('organic amnesia'), although an amnesic state may be temporarily induced by certain drugs. In other instances, an amnesia can occur without any apparent physical cause – a 'functional amnesia' (Kopelman, 2002). Such amnesias are often associated with stress and anxiety (see *Psychogenic amnesia*).

Amnesias have been separated into those that disrupt the ability to acquire and consolidate new information for long-term memory (see *Anterograde amnesia*) and those that cause a failure to recall information prior to the onset of the amnesia (see *Retrograde amnesia*) (Figure A.2). In reality, anterograde and retrograde amnesias often co-occur in the same patient, e.g., in *Korsakoff's disease*.

A diagnostic hallmark of most amnesias is that despite the severe memory problems, other aspects of cognition are spared. As a result, I.Q. is often unaffected. For this reason, the difference between a person's Memory Quotient (M.Q., derived from cognitive batteries such as the Wechsler Memory Scale) and their Intelligence Quotient (I.Q.) is often seen as a key diagnostic feature for anterograde amnesia. Differences of 20 or more points are typical. In contrast with amnesia, the various dementias have much broader, disruptive effects on cognition.

While most amnesic conditions occur in adulthood, it is now known that early damage involving the hippocampus can cause *Developmental amnesia*. This condition has a number of surprising features. Although the acquisition of new episodic information is severely compromised, the acquisition of semantic knowledge, including vocabulary, is relatively spared.

Some drugs can create an amnesic state. Examples include the benzodiazepines, cholinergic antagonists such as scopolamine, as well as *Alcohol*. Epileptic seizures, including those caused by electroconvulsive therapy, can also leave a period of amnesia centred around the seizure. While some organic amnesias are permanent, other amnesic conditions are transient, and the person shows appreciable recovery. An example of the latter is *Transient global amnesia*.

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AMYGDALA – *a limbic brain structure in the anterior part of the medial temporal lobes*

The amygdala, whose functions are primarily linked to emotion, also has important influences on memory and social interactions (Dalgleish, 2004). The amygdala is a complex structure composed of multiple nuclei (Figure A.3). (The term 'nucleus' in this context refers to a distinguishable subregion within a subcortical brain structure). Each amygdala nucleus has a unique array of brain connections. The anatomy of the amygdala is unusual as it is directly connected with a great many cortical and subcortical brain sites, creating a wide hub of influences. Reflecting its many influences, the amygdala contributes to multiple functions, including aspects of memory. One of its functions is to ensure that heightened emotions can facilitate learning and memory.

[Abbreviations of amygdala nuclei and related structures depicted in Figure A.3: ACo, anterior cortical nucleus; AHi, amygdalo-hippocampal area; BL, basolateral nucleus; BLa, anterior subdivision of the basolateral nuclei; BLd, dorsal subdivision of the basolateral nucleus; BLi, intermediate subdivision of the basolateral nucleus; BLv, ventral subdivision of the basolateral nucleus; BM, basomedial nucleus; BMd, dorsal subdivision of the basomedial nucleus; BMv, ventral subdivision of the basomedial nucleus; Ce, central nucleus; Co, cortical nucleus; Coa, anterior subdivision of the cortical nucleus; Cop, posterior subdivision of the cortical nucleus; Fx, fornix; I, intercalated masses; L, lateral nucleus; La, lateral nucleus; Me, medial nucleus; MeA, anterior subdivision of the medial nucleus; MePD, posterodorsal subdivision of the medial nucleus; MePV, posteroventral subdivision of the medial nucleus; Mt, mammillothalamic tract; Ot, optic tract;

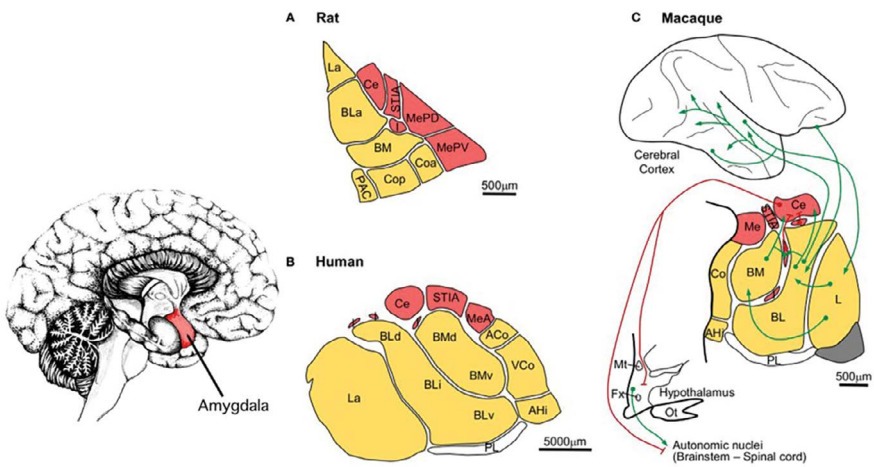

Figure A.3 Location of the human amygdala alongside coronal sections showing its multiple nuclei in the rat (A), human (B), and macaque (C) brain (Ruiz-Cabrera et al., 2023). Some major connections are also depicted. (See main text for abbreviations.)

PAC, periamygdaloid cortex; PL, paralaminar nucleus; STIA, intra-amygdaloid subdivision of the stria terminalis; VCo, ventral subdivision of the cortical nucleus (Ruiz-Cabrera et al., 2023)]

The importance of the amygdala for *Fear conditioning* has been confirmed in studies with rats and mice. These rodent studies led to a model of fear conditioning by Joseph LeDoux in which the amygdala occupies centre stage. In that model, fear-evoking stimuli take both a relatively direct (thalamic) route to the amygdala as well as a longer (cortical) route (LeDoux, 2012). The more direct route to the amygdala allows for more rapid reactions while the longer, slower route enables a greater depth of sensory analysis. Plasticity in the connections between different amygdala nuclei then enables classical conditioning between the fear-evoking unconditioned stimulus and the associated conditioned stimulus (LeDoux, 2012). The lateral and basal amygdala nuclei are seen as key sensory processors in the learning pathway, while the central nucleus is regarded as the final amygdala step. Projections from the central nucleus then coordinate a wide range of autonomic and behavioural reactions to fear-associated stimuli.

The human amygdala is presumed to serve a similar role. As might be expected, people with bilateral amygdala damage, such as that caused by the rare genetic disorder Urbach-Wiethe disease, can show attenuated fear responses and an inability to anticipate threats, despite being able to feel emotions other than fear (Feinstein et al., 2011). Anecdotally, such patients may inadvertently put themselves at greater danger when exploring unfamiliar locations. Formal experiments with Urbach-Wiethe patients reveal a failure to classically condition to those stimuli that predict an upcoming aversive event. As part of this syndrome, patients with amygdala pathology can also show a selective failure to recognize facial expressions of fear. Furthermore, when people with Urbach-Wiethe disease gamble they make more risky decisions as they are less averse to possible bad outcomes (Brand et al., 2007). Other evidence from this rare group of patients points to a wider disruption of emotional processes that need not be confined to fear (Siebert et al., 2003).

Memory consolidation is often heightened when aroused by an emotional experience. The amygdala is a vital part of this consolidation enhancement process (Paré & Headley, 2023). Experiments by James McGaugh with rodents showed that this memory boost is initiated by the release of adrenaline from the adrenal gland, with signals reaching the amygdala via the nucleus of the solitary tract. A crucial next step is the release of noradrenaline within the amygdala. Experiments that block the actions of noradrenaline within the rodent amygdala stop this memory enhancement, highlighting the significance of this interaction (Packard et al., 2021).

A parallel memory enhancement process appears to operate in the human brain (Cahill, 2000). For example, antagonising the neurotransmitter noradrenaline with the drug propranolol blocks the gain in human memory that is normally seen for emotionally arousing events. Furthermore, functional imaging studies show how activity in the human amygdala is increased by emotive events and that the rise in activity correlates with the subsequent recall of that same event (Cahill, 2000). These memory-modulating effects are further influenced by the release of

glucocorticoids (cortisol in humans, corticosterone in rodents), which not only act upon the amygdala but also upon the neocortex and hippocampus. As a result, amygdala damage, e.g., from Urbach-Wiethe disease, can attenuate the memory gain associated with unexpected emotional events. These findings complement other evidence that amygdala activity normally contributes to the aversive memory flashbacks seen in Post-Traumatic Stress Disorder. One surprising source of evidence (Koenigs & Grafman, 2009) comes from the finding that those Vietnam war veterans unfortunate enough to have suffered amygdala damage had lower than expected rates of post-traumatic stress disorder (PTSD).

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ANTEROGRADE AMNESIA – *the failure to encode, consolidate, or retrieve new information that would normally reside in explicit long-term memory*

Some, but not all, amnesias have an anterograde component. The term 'anterograde' refers to the difficulty with learning and remembering new information experienced *after* the onset of the amnesia. Other cognitive abilities are spared, meaning that I.Q. levels are typically preserved (Figure A.4). Although anterograde amnesias can be induced by certain drugs, this section focuses on the consequences of brain injury and disease.

The loss of new learning in anterograde amnesia is not global. Patients with anterograde amnesia show a sparing of implicit memory (Kopelman, 2002). Examples include priming, habituation, classical conditioning, and perceptual-motor skill learning. In addition, short-term memory is largely intact. In contrast, explicit long-term memory is much affected, most obviously episodic memory. Some aspects of working memory may also be affected, such as when there is a demand for

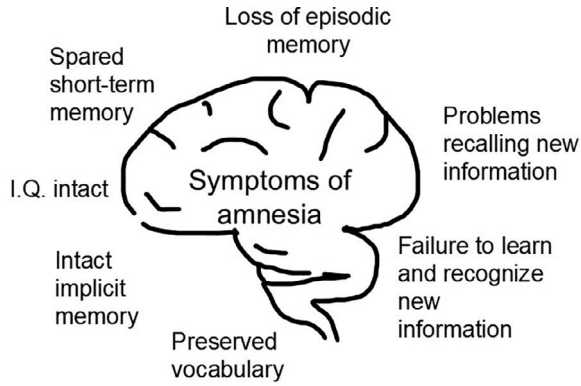

Figure A.4 Anterograde amnesia. Core symptoms of anterograde amnesia.

high-precision, information binding. The pattern of memory loss and memory sparing in anterograde amnesia reinforces the idea that there are qualitatively different forms of memory which depend on different brain structures.

Anterograde amnesia is not an all-or-none condition, as its severity can vary depending on the location and the extent of brain pathology. Many anterograde amnesias are associated with pathology in either the medial temporal lobe ('temporal lobe amnesia') or the medial diencephalon ('diencephalic amnesia'), although anterograde amnesias can arise from damage to other sites (Ferguson et al., 2019). Temporal lobe amnesia can be caused by conditions such as vascular strokes, herpes encephalitis, hypoxia (shortage of oxygen), tumours, and autoimmune limbic encephalitis. Bilateral hippocampal pathology appears to be both necessary and sufficient for temporal lobe amnesia (Spiers et al., 2001). Meanwhile, diencephalic amnesia is associated with thalamic strokes and tumours. *Korsakoff's disease*, which is most typically seen in alcoholics, is a further form of diencephalic amnesia. The core pathology in diencephalic amnesia is thought to involve the mammillary body-anterior thalamic axis, often augmented by additional thalamic and white matter damage (Aggleton & O'Mara, 2022).

The cognitive features of temporal lobe and diencephalic amnesia are highly similar, as they both show the same profile of lost and spared memory. Tests on rates of forgetting also point to their similarities. The implication is that both regions are critical parts of a common, interactive network that is vital for episodic memory, with different areas making complementary contributions. Consistent with this view is how medial temporal and medial diencephalic sites are interconnected via tracts such as the fornix and cingulum bundle (Aggleton & Brown, 2006). The idea that temporal lobe and diencephalic amnesias arise from damage to a shared network is further supported by MRI studies that reveal how organic amnesias share common nodal pathways centred on the retrosplenial cortex and the adjacent subiculum (Ferguson et al., 2019). Both of these sites are highly interconnected with the hippocampus (temporal lobe) and the anterior thalamic nuclei (diencephalon).

The sparing of short-term memory in anterograde amnesia helps to explain why amnesics can successfully complete I.Q. tests and why short-term memory is seen as distinct from long-term memory, despite their need to interact. The growing realization that some forms of long-term memory are also spared in anterograde amnesia added to other evidence supporting the separation between explicit and implicit long-term memory. *Explicit* memories are those for which we have conscious insight and can be described when retrieved (semantic and episodic memories). In contrast, *Implicit* memories affect our actions, yet we cannot consciously interrogate their nature (examples include priming, classical conditioning, habituation, and procedural leaning). While anterograde amnesias severely disrupt episodic memory, they typically spare new implicit long-term learning. The acquisition of new semantic memories (shared facts and vocabulary) is also affected, although some limited learning is often seen.

For decades there has been debate over whether anterograde amnesia is caused by problems with encoding, consolidation, or retrieval (Kopelman, 2002). Trying to separate these elements proved challenging given that poor encoding will lead to inferior consolidation and, consequently, difficulties with retrieval. In reality, there is strong evidence that all three processes can be disrupted, although much of the recent focus has been on how the hippocampal formation and its allied regions work together during encoding to create the unique context (what? where? when?) that is the hallmark of each episodic memory. While the hippocampal formation is also involved in memory retrieval, the extent and duration of that contribution has been disputed (see *Retrieval*).

While the recall of new episodic information is consistently affected by anterograde amnesia, the impact on recognition memory can vary. In a minority of amnesic cases, there is a relative sparing of recognition memory compared to recall, even when the memory tasks are of comparable difficulty. The favoured explanation is that these amnesics have more selective pathology, so that the signalling of stimulus familiarity is spared, even though the ability to recollect that same stimulus is lost (Vann et al., 2009). This pattern fits with dual-process models of *Recognition memory* which suppose that recognition decisions are supported by two independent types of information, i) feelings of familiarity for the target and ii) the explicit recall of the target or associated information (Yonelinas et al., 2010).

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ASSOCIATIVE LEARNING – *the ability of organisms to make connections between related events in their environment*

Associative learning is often regarded as the archetypal form of learning displayed by people and other animals. The term refers to our ability to learn contingencies in our environment. These contingencies can relate to learnt associations between different stimuli or learnt associations between a stimulus and a response. For example, when walking, I step aside if I hear a bicycle bell as that distinctive sound is linked (associated) with an approaching cyclist.

Historically, the study of associative learning was driven forward by two paradigms, *Classical conditioning* and *Instrumental conditioning* (or operant conditioning). Meanwhile, the term 'non-associative' learning was applied to processes such as habituation and sensitization. The latter division has, however, been challenged because both habituation and sensitization can be affected by historic associations held by the observer, as well as being influenced by the context in which these processes take place. In other words, associative learning can seemingly affect these 'non-associative' forms of learning (Dissegna et al., 2021).

The term associative learning is very broad as it covers the many ways in which organisms acquire information about the relationships between different events. As a result, the study of associative learning incorporates stimulus–stimulus (S–S learning), stimulus–response (S–R learning), response–response (R–R learning), and response–reinforcement learning. In addition, the term has been applied to how we acquire knowledge by making connections in our minds between separate items of information.

Reflecting its fundamental importance, there has been considerable interest in determining those conditions that encourage associative learning. Identifying these conditions has enormous theoretical and practical significance. For a long time, temporal contiguity and spatial contiguity were seen as the primary determinants of associative learning. In other words, events that are overlapping or close in time and space may be rapidly associated while events that are separated will struggle to be linked. This general rule seemed appropriate irrespective of whether the learning involved associations between stimuli (S–S) or associations between stimuli and responses (S–R).

But, by the 1960s and 70s it became clear that the emphasis on contiguity was incomplete. For example, when multiple cues are present during learning, the strength of conditioning to one cue can limit the amount of learning to the other cues (see *Blocking*). Famously, in 1972, Rescorla and Wagner proposed that the amount of learning reflects the discrepancy between what the individual expected (predicted) and what occurred (see Soto et al., 2023). The greater the *Prediction*

error, the greater the potential for new learning. Conversely, very little new learning would occur if the subject had correctly anticipated what occurred. Put another way, the rate of learning reflects how surprised the subject is by the outcome (the more surprised, the more learning).

In addition, the amount of conditioning to a stimulus has a cap or limit. In this way, Rescorla and Wagner could explain why, when multiple cues are present during learning, the strength of conditioning to one cue will limit the possible learning to other cues (cue competition). Similarly, phenomena such as 'blocking' could now be explained. Other key factors in their model concerned the individual salience of the various cues in the environment, with greater conditioning occurring to more salient cues ('Overshadowing'). Revisions to this model include the 'Sometimes Opponent Model' (SOP) of Wagner that adds a focus on stimulus representations (Vogel et al., 2019).

Despite subsequent critiques and revisions of the Rescorla-Wagner model, the concept of 'prediction error' has become a mainstay across multiple aspects of computational psychology and neuroscience. One key finding, from 1997 by Wolfram Schulz and colleagues, was the discovery that dopaminergic neurons in the ventral tegmental area show activity patterns that match the differences between expected and received rewards, i.e., the prediction reward error (Schultz, 2017).

A related issue concerns the interplay between attention and associative learning. One set of models assumes that attention is biased towards those stimuli that reliably predict their consequences ('learned predictiveness'). The strength of this attention is modulated by the value of the outcome, so that high-value predictors receive the most attention. Intuitively this relationship makes sense. But, a very different concept, again based on prediction error, is that uncertainty can lead to high levels of attention, which promotes learning. In other words, individuals pay added attention to those stimuli with an uncertain or non-existent history, thereby, enhancing cue associability (Holland & Schiffino, 2016). Evidence for both mechanisms has come from studies of animal learning, resulting in hybrid models that allow for the two operations to exist in parallel (Le Pelley et al., 2016).

Other refinements to associative learning principles included the realization that organisms are not a blank slate. Rather, our brains are predisposed to process and associate certain kinds of information. Examples include the phenomena of *Imprinting* (such as when a new-born forms a long-lasting bond to another, usually its parent) and *Conditioned taste aversions* (when we link a taste with a nauseous experience) (see also *Adaptive memory*).

Finally, associative learning (typically classical conditioning) has been used to test for 'Minimal Cognition' in simple organisms. While there are increasing examples of associative learning across many invertebrate phyla, two groups without nervous systems (porifera [sponges] and placozoa) show no evidence of such learning (Loy et al., 2021). Likewise, numerous studies of unicellular organisms, such as paramecia and amoeba, have failed to deliver convincing evidence of associative learning, although habituation and sensitization are observed in a range of unicellular organisms. Turning to plants, a favoured model is the 'sensitive plant' (*Mimosa pudica*), as its leaves will retract on being touched. Despite evidence for